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Synthesis of *dl*-α-Lipoic Acid from a Butadiene Telomer

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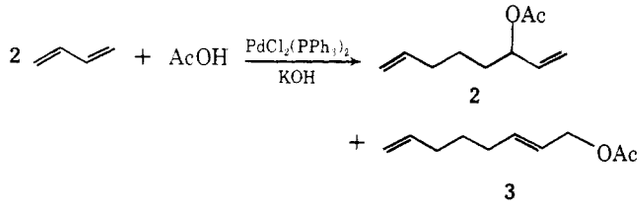
Received April 7, 1978

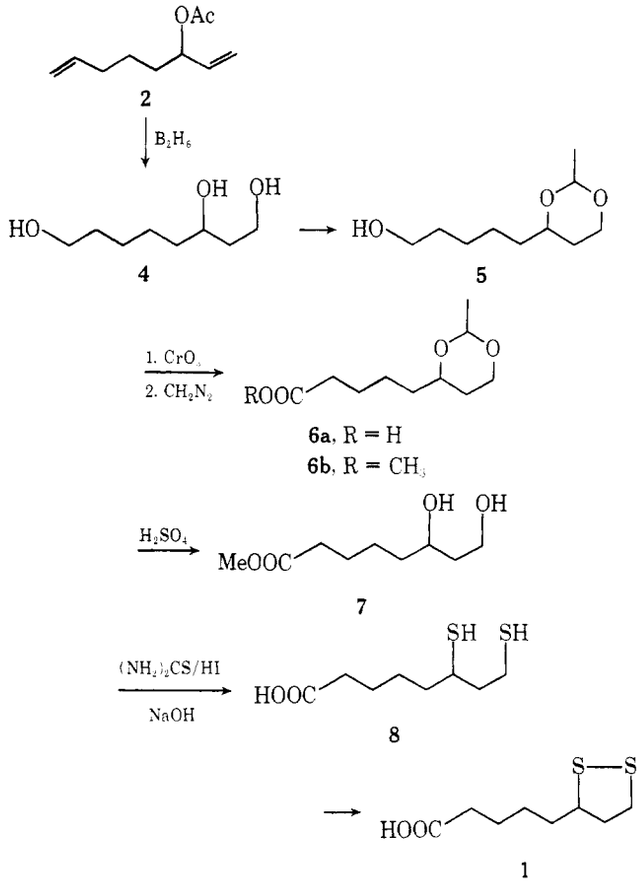
α-Lipoic acid has been recognized as a cofactor involved in the biochemical decarboxylation of α-keto acids and as a growth factor for a variety of microorganisms.[1] This naturally occurring sulfur containing vitamin was isolated by Reed et al.[2] from liver in 1951 and identified as 1,2-dithiolane-3-valeric acid (1). Because of its important physiological properties, numerous synthetic studies of this acid have been carried out.[1]

In designing an efficient synthesis of *dl*-α-lipoic acid, two problems have to be considered. The first one is the selection of proper building blocks for the eight-carbon chain, and there are still many possibilites. In the first synthesis by Bullock et al.,[3] ethylene and adipic acid half ester acid chloride were used as building blocks of the eight-carbon chain. In another synthesis by Braude et al.,[4] 6-heptenoic acid was subjected to Prins reaction. Other starting materials were 2-hydroxyethylanisole[5] and 2-acetoxyethylcyclohexanone[6] which were cleaved to give the eight-carbon chain with necessary functional groups. The second problem in the α-lipoic acid synthesis is the method of forming the dithiolane system. For this purpose, usually 1,3-diols, tosylates, and halides were converted to the dithiols by the reaction of sulfur compounds such as sodium disulfide,[7] thioacetic acid,[8] benzylmercaptane,[8] and thiourea.[3-5]

We now wish to report a new simple synthetic method for *dl*-α-lipoic acid using a butadiene telomer as a very suitable starting material, offering a new solution to the first problem mentioned above. Palladium-catalyzed telomerization of butadiene with various nucleophiles affords a number of useful telomers. In our continuous effort to utilize these telomers in organic synthesis, we have already synthesized a number of natural products starting from various butadiene telomers. In the present synthesis of *dl*-α-lipoic acid, we used 3-acetoxy-1,7-octadiene (**2**), a telomer obtained easily with 1-acetoxy-2,7-octadiene (**3**) from butadiene and acetic acid.[9,10] The ester **3** can be rearranged to **2** with the palladium catalyst.



We have already utilized these easily available telomers for simple syntheses of 2,15-hexadecanedione,[11,12] 1-octen-3-ol (Matsutake alcohol),[13,14] and diplodialide.[15] The compound **2** has the eight-carbon chain necessary for *dl*-α-lipoic acid synthesis. In addition, its functional groups, namely two double bonds and one acetoxy group, are located at the right positions and very suitable for conversion to *dl*-α-lipoic acid. The synthesis has been carried out by the following sequence of reactions.



The first step of the synthesis is hydroboration of two terminal double bonds. At first the reaction was carried out with 9-borabicyclo[3.3.1]nonane. Although the hydroboration proceeded smoothly with this hydroborane, the separation of cyclooctanediol, formed by the oxidation of the reagent, from desired 1,3,8-octanetriol (**4**) was not easy. Therefore the hydroboration of **2** was carried out using B_2H_6 to give the triol **4** which is very soluble in water. The triol was isolated using a continuous extractor. Then in order to differentiate one hydroxy group from the 1,3-diol system, the latter was protected by six-membered acetal formation using paracetaldehyde to afford **5** in 64% yield from **2**. The oxidation of the unprotected terminal alcohol was carried out with Jones reagent to give carboxylic acid **6a** in 73% yield. Although the oxidation was carried out under acidic conditions, the protecting group of the 1,3-diols was not attacked. The carboxylic acid was methylated with diazomethane in order to avoid lactone formation in the next step. The protecting group was removed by heating with sulfuric acid in dry methanol to give methyl 6,8-dihydroxyoctanoate (**7**) in 92% yield. The ester **7** is a known compound and the conversion of the ester to *dl*-α-lipoic acid has been carried out already. Following the method of the literature,[3] the ester was treated with thiourea in hydroiodic acid and 6,8-dimercaptooctanoic acid (**8**) was isolated in 80% yield. The final step is the oxidative ring closure to form the dithiolane ring by bubbling oxygen in the presence of ferric chloride. By this way, *dl*-α-lipoic acid was obtained as a yellow crystalline compound which was identified by its melting point and spectral data.

Experimental Section

All boiling points and melting points were uncorrected. IR spectra were recorded as neat films on a JASCO IR-2 spectrometer. NMR spectra were recorded in CCl_4 on a HITACHI R-24 A, (60 MHz) with Me_4Si as an internal standard.

0022-3263/78/1943-3606$01.00/0

3-Acetoxy-1,7-octadiene (2). A mixture of $PdCl_2(PPh_3)_2$ (400 mg, 0.57 mmol), KOH (200 mg, 3.56 mmol), acetic acid (21.0 g, 0.35 mol), and triethylamine (35.4 g, 0.35 mol) was placed in a 100-mL autoclave and then butadiene (29 mL, 0.35 mol) was introduced. The autoclave was placed in an oil bath kept at 90 °C and stirred with a magnetic stirrer. After 10 h, ether (20 mL) was added to the resulting mixture and the solution was acidified with 3 N HCl and washed with brine. The organic layer was dried over magnesium sulfate and evaporated. The crude oil was distilled to give a mixture of 3-acetoxy-1,7-octadiene (2) and 1-acetoxy-2,7-octadiene (3) (1:2.7) (25 g, 85% based on butadiene). The fractional distillation of the mixture gave pure 3-acetoxyl-1,7-octadiene (2) (92 °C (24 Torr)): NMR (CCl_4) δ 1.52 (4 H, m), 1.80–2.27 (2 H, m), 2.00 (3 H, s), 4.78–6.13 (7 H, complex m); IR 1742, 1640, 1375, 1242 cm^{-1}.

1,3,8-Octanetriol (4). A solution of 3-acetoxy-1,7-octadiene (2) (3.36 g, 20.0 mmol) in dry tetrahydrofuran (15 mL) was placed in a flask under nitrogen atmosphere. Next the flask was placed in an ice bath and a 2.4 M solution of B_2H_6 in tetrahydrofuran (15 mL) was added slowly. The solution was stirred for 2 h at room temperature. A mixture of 5 N NaOH (15 mL) and 28% hydrogen peroxide (10 mL) was added dropwise to the flask at 0 °C and the mixture was stirred for 3 h at room temperature. The reaction mixture was poured into a cooled aqueous sodium thiosulfate solution to remove excess hydrogen peroxide. The solution was concentrated to 10 mL and continuous extraction with ethyl acetate was carried out. The extract was evaporated to give a crude triol 4 (2.59 g). The triol 4 was used in the next step without purification.

1-Hydroxy-5-(2-methyl-1,3-dioxan-4-yl)pentane (5). A mixture of the crude triol 4 (2.59 g), paraldehyde (5 mL), and a catalytic amount of *p*-toluenesulfonic acid dissolved in dry dichloromethane (10 mL) was placed in a flask under nitrogen atmosphere. The reaction was carried out for 2 h at room temperature. An aqueous sodium bicarbonate solution was added to the resulting mixture. The solution was extracted with dichloromethane and the extract was washed with brine. Dichloromethane and excess paraldehyde were removed under reduced pressure to give a crude oil. The oil was purified by column chromatography (silica gel, *n*-hexane/ether, 5:1) to afford alcohol 5 (2.40 g, 63.8% from 2): NMR (CCl_4) δ 1.24 (3 H, d, J = 5 Hz), 1.40 (10 H, broad), 3.31 (1 H, s), 3.40–4.23 (5 H, m), 4.65 (1 H, q, J = 5 Hz); IR 3450, 2945, 2870, 1135, 960 cm^{-1}.

Methyl 5-(2-Methyl-1,3-dioxan-4 yl)valerate (6b). The alcohol 5 (1.88 g, 10 mmol) dissolved in acetone (5 mL) was placed in a flask at 0 °C. Then Jones reagent (CrO_3–H_2SO_4) was added to the flask slowly. The color of a solution turned to green. The Jones reagent was added dropwise until its red-brown color remained. After water was added to the flask, the resulting mixture was extracted with ether. An aqueous sodium carbonate solution was added to the extract to remove neutral compounds. The aqueous layer was extracted with ether and acidified with 3 N HCl. The solution was extracted with dichloromethane and the extract was dried over magnesium sulfate. The solvent was removed to give the desired carboxylic acid **6a** (1.46 g, 72%): NMR (CCl_4) δ 1.22 (3 H, d, J = 5 Hz), 1.48 (8 H, broad), 2.32 (2 H, m), 3.20–4.22 (3 H, m), 4.60 (1 H, q, J = 5 Hz), 10.67 (1 H, s); IR 1720 cm^{-1}.

The crude carboxylic acid was converted to the methyl ester **6b** with diazomethane. The product was purified by column chromatography (silica gel, *n*-hexane/ether, 10:1) to give the pure methyl ester **6b** (1.40 g, 65% from 5): NMR (CCl_4) δ 1.21 (3 H, d, J = 5 Hz), 1.42 (8 H, broad), 2.25 (2 H, m), 3.10–4.20 (3 H, m), 3.60 (3 H, s), 4.55 (1 H, q, J = 5 Hz); IR 2950, 1740 cm^{-1}.

Methyl 6,8-Dihydroxyoctanoate (7). A mixture of the protected product **6b** (1.00 g, 4.63 mmol) and dry methanol (50 mL) was refluxed in the presence of a catalytic amount of concentrated sulfuric acid. After 24 h, the solution was concentrated to 10 mL and the residue was diluted with water. The solution was extracted with ether. From the extract, unchanged ester (258 mg) was recovered. The aqueous solution was neutralized with sodium hydrogen carbonate solution and concentrated under reduced pressure. The residue was extracted with boiling ethyl acetate. The extract was dried over magnesium sulfate and evaporated to give methyl 6,8-dihydroxyoctanoate (7) (605 mg, 92.8% based on the consumed ester **6b**): NMR (CCl_4) δ 1.46 (8 H, m), 2.28 (2 H, t), 3.49–4.15 (5 H, m), 3.60 (3 H, s); IR 3370, 2925, 1740 cm^{-1}.

6,8-Dimercaptooctanoic Acid (8). A mixture of methyl 6,8-dihydroxyoctanoate (7) (500 mg, 2.63 mmol), thiourea (1.8 g, 23.6 mmol), and 57% HI (4 g) was heated under reflux for 24 h. After cooling, KOH (4 g) in water (10 mL) was added and the mixture was refluxed for 12 h under nitrogen. The mixture was then extracted with ether, acidified with 3 N HCl, and extracted with dichloromethane. The extract was washed with water, dried over magnesium sulfate, and evaporated to give a yellow oil (522 mg). The oil was distilled under reduced pressure (170–175 °C bath temperature (8.3×10^{-2} Torr)) to give 6,8-dimercapotooctanoic acid (8) (438 mg, 80%): NMR δ 3.08 (2 H, t, J = 6 Hz), 3.49 (1 H, m), 11.31 (1 H, s); IR 2925, 1710, 1410, 1285 cm^{-1}.

dl-α-Lipoic Acid (1). A mixture of dithiol acid 8 (190 mg, 0.913 mmol) and water (6 mL) containing NaOH (31 mg, 0.775 mmol) and ferric chloride (2 mg) was placed in a flask. The color of the solution turned to dark red. A stream of oxygen was bubbled through the solution until the reddish color changed to pale yellow. After 9 h, the resulting pale yellow solution was washed with dichloromethane. The aqueous layer was acidified with 3 N HCl and extracted with dichloromethane. The extract was dried over magnesium sulfate and evaporated to give a yellow oil, which solidified upon trituration with pentane. Crystallization from hexane gave *dl*-α-lipoic acid (1) (132 mg, 70%) as yellow needles: mp 60–61 °C (lit. mp 60 °C,[4] 60–60.5 °C,[5] 61 °C,[3] 61–62 °C[6,8]); NMR (CCl_4) δ 1.60 (8 H, broad), 2.37 (2 H, m), 3.08 (2 H, t, J = 6 Hz), 3.50 (1 H, m), 12.00 (1 H, s); IR 3300–2400, 1690, 1250, 945 cm^{-1}.

Acknowledgment. This work was supported financially by the Grant-in-aid administered by the Ministry of Education, Japanese Government (203510).

Registry No.—**1,** 1077-28-7; **2,** 66859-02-7; **3,** 3491-27-8; **4,** 66859-03-8; **5,** 66859-04-9; **6a,** 66859-05-0; **6b,** 66859-06-1; **7,** 66859-07-2; **8,** 7516-48-5; butadiene, 106-99-0; acetic acid, 64-19-7.

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Stereoselective Synthesis of 1-Substituted (*E,E*)- and (*E,Z*)-2,4-Decadienyl Derivatives

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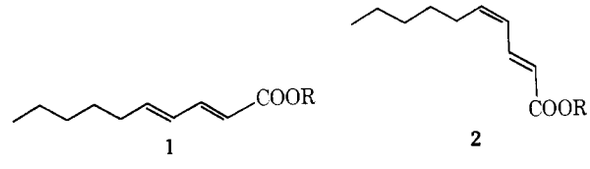
Received March 14, 1978

Recently we required the ethyl esters of (*E,E*)-2,4-decadienoic acid (1, R = H) and the corresponding (*E,Z*)-2,4-decadienoic acid (2, R = H). Since these compounds were to serve as starting materials in a synthesis of the prostaglandin nucleus, it was imperative that our syntheses be stereoselec-



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